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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/058,546	04/10/98	GUNZBURG W	GSF98-02A

021005
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EXAMINER	
WILSON, M	
ART UNIT	**PAPER NUMBER**
1633	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/058,546	Applicant(s) Gunzberg et al.
	Examiner Wilson, Michael C.	Group Art Unit 1633

☒ Responsive to communication(s) filed on *Nov 29, 1999* .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-16 and 18-32* is/are pending in the application.

Of the above, claim(s) *5-7, 12, 18, 24, 25, 29, and 30* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-4, 8-11, 13-16, 19-23, 26-28, 31, and 32* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The Information Disclosure Statement filed 5-22-99, paper number 5, has been considered and made of record. Claim 17 has been canceled. Applicant's arguments filed 11-29-99, paper number 8, have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restriction

1. Applicant's affirmation of the election of Group I, claims 1-4, 8-11, 13-17, 19-23, 26-28, 31 and 32, in Paper No. 8, filed 11-29-99, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-16 and 18-32 are pending in the instant application. Claims 5-7, 12, 18, 24, 25, 29 and 30 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 8. Claims 1-4, 8-11, 13-16, 19-23, 26-28, 31 and 32 are under consideration in the instant application as they relate to DNA. Claims with limitations directed toward antisense or DNA will be considered only as they relate to DNA.

Claim Rejections - 35 USC § 112

2. Claims 1, 3, 4, 15, 16, 19-23, 26-28, 31 and 32 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way

as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record set forth in the office action of 5-24-99.

Feldman et al. (1995, Fundamental & Clinical Pharmacology, Vol. 9, pages 8-16; page 13, column 1, second paragraph) and Crystal (1995, Science, Vol. 270, page 404-410; page 409, column 1, line 22 through column 2, line 34) both of record reflect the state of the art of gene therapy at the time of filing. While Feldman and Crystal do not discuss the *in vitro* human bladder carcinoma assay used in the instant invention, Feldman and Crystal discuss using retroviral vectors encoding therapeutic proteins to treat diseases such as restinosis and cancer as claimed in the instant application (claims 22, 23 and 28). The references teach that it is unpredictable whether therapeutic effects can be obtained against restinosis, cancer or any other disease using gene therapy because of the low efficiency of cells expressing the transgene, low transfection efficiency, the lack of target specificity, the lack of sustained expression and the lack of predictable expression of genes in humans. It would require one of skill undue experimentation to determine the promoter, dosage, route and mode of delivery and level of expression required to treat restinosis, breast cancer or any other disease using the retroviral particles disclosed in the instant invention.

Applicants argue that the specification teaches human bladder carcinoma transfected with retroviral particles encoding SDI-1 *in vitro* had more cells in G_0/G_1 (page 26, lines 20-22); therefore, applicants argue it is reasonable to expect such retroviral particles or capsules containing cells producing the retrovirus can be used to treat diseases or disorders responsive to

SDI-1. Applicants argument is not persuasive. The specification does not provide adequate guidance correlating the results obtained *in vitro* to results obtained *in vivo* in such a way that one of skill would have a reasonable expectation in obtaining a therapeutic level of expression of SDI-1 such that cancer or restinosis could be treated. While an exact correlation is not required to enable an invention (page 7, line 20 of arguments), a reasonable correlation must be provided. The specification does not teach the level of SDI-1 required to obtain a therapeutic effect, the dosage, route of administration or the desired therapeutic effect such that one of skill would be able to determine how to use the retroviral vector as a pharmaceutic composition (claims 19-20). In particular, it is unclear what therapeutic effect can be obtained by obtaining more cells in G_0/G_1 or how bladder carcinoma correlates to breast cancer (claim 23) or restinosis (claims 22 and 28). Therefore, the specification does not provide a reasonable correlation between obtaining bladder carcinoma in G_0/G_1 *in vitro* and *in vivo* uses of the retroviral particles.

Applicants argue the specification teaches that the dosage depends upon the mode of administration, form in which delivered, etc. The dosage, mode of administration and vehicle of delivery are parameters which are essential to the invention and would require undue experimentation to determine given the unpredictability in the art. The specification does not enable any pharmaceutic compositions, use of a retroviral vector for treatment of disease or methods of introducing retroviral particles for the purpose of therapy as claimed.

Applicants argue that one of skill in the art would be able to determine amino acids 1-71 or 42-58 of the human SDI-1 as claimed in claims 3 and 4 given the teachings provided in the

specification because the specification states that SDI-1 is described in WO-A1-95/06415 (page 8, lines 20-21). Applicants have enabled one of skill to determine amino acids 1-71 or 42-58 of the human SDI-1 gene disclosed in WO 95/06415 but not any other human SDI-1, WAF1, CIP1, PIC1 or p21 sequence disclosed in the art (see page 2, line 2 of specification). It is not clear that any other amino acids of human SDI-1, WAF1, CIP1, PIC1 or p21 would have the same amino acid sequence or function as amino acids 1-71 or 42-58 described in WO 95/06415. The amino acid sequence encoding human SDI-1, WAF1, CIP1, PIC1 or p21 varies in the art; therefore, one of skill would not be able to determine what applicants consider amino acids 1-71 or 42-58 of SDI-1 other than the sequence disclosed in WO 95/06415.

Applicants argue routine methods could be used to determine functionally equivalent analogues or fragments of SDI-1. Applicants argument is not persuasive. The specification has not taught any method to identify functionally useful analogues or fragments of the human SDI-1 gene taught in WO 95/06415. Such methods are not routine and are considered essential to determine functionally equivalent analogues or fragments as claimed.

Applicants argue the encapsulated cells and a pharmaceutical composition comprising packaging cells are enabled because the *in vitro* bladder carcinoma example in the specification enables *in vivo* therapeutic uses of such compositions. Applicants argument is not persuasive. The only disclosed use for encapsulated cells and pharmaceutical compositions in the specification is for administering the cells *in vivo* to obtain therapeutic effects (page 8, lines 5-19). The administration of replication competent retroviral packaging cells would most likely result in

toxic, non-therapeutic results. Retroviral packaging cells are known to produce replication competent retroviral particles which, upon introduction to an individual, would prevent obtaining therapeutic effects. The specification does not provide adequate guidance such that one of skill could prevent production of replication competent retroviral particles or administer retroviral packaging cell lines such that a therapeutic effect could be obtained. The specification does not teach the dosage, route of administration, level of retroviral particles secreted or level of SDI-1 expression required *in vivo* to use encapsulated retroviral packaging cells to treat any disease.

Claim 2 recites the new limitation of a vector which carries a DNA sequence. The specification has not provided adequate guidance for vectors to carry DNA. Vectors may comprise DNA but do not carry DNA as claimed.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite limitations wherein the recombinant retroviral particle is administered as an injection or by implantation of a packaging cell line. However, the claims refer to claim 28 which is limited to delivery of a packaging cell line. It is unclear whether applicants intend to claim administering retroviral particles or retroviral packaging cells.

Claim Rejections - 35 USC § 102

4. Claims 1-4 and 9 remain rejected under 35 U.S.C. 102(b) as being anticipated by Tsang et al. (1994, Vaccine Res., Vol. 3, page 183-193) for reasons of record set forth in the office action of 5-24-99, paper number 4.

Tsang et al. teach a method of making retroviral particles comprising DNA encoding human p21 ras and mutants of p21 using packaging cells lines equivalent to the producer cells claimed (page 185, second paragraph). Tsang et al. anticipate the limitation of human SDI-1 since human p21 is involved in the cell cycle (page 184, line 2). The particles taught by Tsang et al. encodes amino acids 1-71 and 42-58, as in claims 3 and 4. Applicants argue Tsang et al. does not relate to the SDI-1 protein which inhibits cell proliferation claimed in the instant invention. Applicants argument is not persuasive. SDI-1 is equivalent to p21 (page 2, line 2 of the specification). Claims 1-4 and 9 do not require that the protein inhibit cell proliferation. Therefore, Tsang et al. meet all the limitations of the claims.

Claim Rejections - 35 USC § 103

5. Claims 1-4, 8, 13, 14, 19, 26-28, 31 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller et al. (1989, Biotechniques, Vol. 7, pages 980-990) or Price et al. (1987, PNAS, USA, Vol. 84, pages 156-160) in view of Nabel et al. (US Patent 5,863,904, Jan 26, 1999).

Methods of making retroviral particles were well known to the ordinary artisan at the time of filing of the instant invention as taught by Miller et al. and Price et al. Miller et al. teach a method of producing retroviral particles comprising transfecting packaging cells, PA317, with a retroviral vector encoding β-gal with a 5' LTR (see page 981, column 1, column 3). The PA317 packaging cell line taught by Miller et al. is considered equivalent to the producer cell claimed (claim 1) and the PA317 cells used in the instant invention (page 28, line 9). Price et al. teach a method of producing BAG retroviral particles using the packaging cell line NIH 3T3 (page 156, column 2, line 18). NIH 3T3 are equivalent to the producer cells claimed because both have a DNA construct coding for proteins for packaging. The BAG retrovirus is equivalent to the retrovirus used in the instant invention (page 22, line 17). Miller et al. and Price et al. do not teach the method of making retroviral particles encoding SDI-1 or producer cells transfected with a retroviral vector encoding SDI-1.

However, at the time of filing, Nabel et al. teach using retroviral vectors comprising the gene encoding human p21 to accumulate cells in G_o/G_1 (see abstract; column 3, line 10; column 4, line 60). The gene encoding p21 taught by Nabel et al. is considered equivalent to SDI-1 as claimed because both SDI-1 and p21 cause cells to accumulate in G_o/G_1, because the specification states SDI-1 is also described as p21 (page 2, line 2) and because Nabel et al. states SDI-1 is equivalent to p21 (column 1, lines 22-23). Nabel et al. teach administering the viral vectors encoding p21 to treat restinosis (see claims) or breast cancer (column 5, line 10) which is equivalent to claim 28. Claims 3 and 4 are obvious in view of Nabel et al. because the p21 taught

by Nabel et al. comprises amino acids 1-71 and 42-58 of SDI-1 as claimed. Nabel et al. teaches producing viral particles in human 293 packaging cells which makes the human producer cells in claim 14 obvious (column 6, line 32). The limitations of injecting the retroviral particle directly to the site of the tumor (claim 31, line 9) and a porus capsule (claim 32, line 12) are obvious in view of Nabel et al. who claim direct injection (claim 1) and encapsulating the viral vector (claim 2).

It would have been obvious to one of ordinary skill at the time the instant invention was made to produce the retroviral vector taught by Nabel et al. using the method taught by Miller et al. or Price et al. One of ordinary skill would have recognized that the retroviral vector taught by Nabel et al. encoding p21 had to be produced using methods such as those taught by Miller et al. or Price et al. One of ordinary skill would have been motivated to produce retroviral vectors encoding p21 as taught by Nabel et al. using the methods taught by Miller et al. or Price et al. to treat disease. Additional motivation is provided by Miller et al. by stating the retrovirus can be used *in vivo* (page 989, last sentence) and by Price et al. by demonstrating the retroviral particles can be used to deliver genes of interest *in vivo* (page 157, column 1, fourth paragraph). The method of administering retroviral particles (claims 26-28, 31 and 32) is obvious in view of the teachings of Nabel et al. and Miller et al. or Price et al. because Price et al. suggests using retroviral particles to deliver the gene of interest and because delivery of retroviral particles was commonly performed *in vivo*. One of ordinary skill would have had a reasonable expectation of success in obtaining the claimed invention because methods of producing retroviral vectors,

packaging cells and methods of administering retroviral particles were well known at the time of filing.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

6. Claims 1 and 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller et al. (1989, Biotechniques, Vol. 7, pages 980-990) or Price et al. (1987, PNAS, USA, Vol. 84, pages 156-160) in view of Nabel et al. (US Patent 5,863,904, Jan 26, 1999) as applied to claims 1-4, 8, 13, 14, 19, 26-28, 31 and 32 above, and further in view of Haertig et al. (1993, J. Virology, Vol. 67, pages 813-821).

Miller et al. and Price et al. teach methods of producing retroviral particles comprising transfecting packaging cells PA317 with a retroviral vector encoding β-gal with a 5' LTR (see page 981, column 1, column 3 of Miller et al.) or packaging cells NIH 3T3 (page 156, column 2, line 18 of Price et al.) (see 103 rejection above). Miller et al. and Price et al. do not teach the method of making retroviral particles encoding SDI-1 or producer cells transfected with a retroviral vector encoding SDI-1. Nabel et al. teach using retroviral vectors comprising the gene encoding human p21 to accumulate cells in G_0/G_1 (see abstract; column 3, line 10; column 4, line 60). The gene encoding p21 taught by Nabel et al. is considered equivalent to SDI-1 as claimed because both SDI-1 and p21 cause cells to accumulate in G_0/G_1, because the specification states SDI-1 is also described as p21 (page 2, line 2) and because Nabel et al. states SDI-1 is equivalent

to p21 (column 1, lines 22-23). Miller et al. or Price et al. taken with Nabel et al. do not teach using the MMTV regulatory elements.

However, at the time of filing, Haertig et al. teach the MMTV regulatory elements which can be used to create a chimeric retroviral vector to obtain mammary cell-specific expression of the gene of interest (see page 819, column 2, first full paragraph; page 820, column 1, last full paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of making a retroviral particle taught by Miller et al., Price et al. and Nabel et al. with the MMTV regulatory elements taught by Haertig et al. One of ordinary skill would have been motivated to deliver retroviral vectors to breast cancer as suggested by Nabel et al. (column 5, line 10) using the MMTV regulatory elements taught by Haertig et al. because Haertig et al. the MMTV elements are mammary specific. One of ordinary skill would have been motivated to target breast tissue to improve p21 expression in breast cancer and to obtain a greater therapeutic effect. One of ordinary skill would have had a reasonable expectation of success in obtaining the method claimed using the teachings of Miller et al., Price et al., Nabel et al. and Haertig et al. because methods of producing retroviral particles and of methods of inserting promoters to retroviral vectors were common at the time of filing.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

The art rejections above are made in view of applicants amendments to the claims. Applicants arguments regarding the previous art rejection are addressed as they relate to the remaining references as follows:

Applicants argue Nabel et al. does not teach Applicants' claimed invention because Nabel et al. teach producing adenovirus using 293 packaging cells which causes lysis. Applicants argument is not persuasive. The 293 packaging cells of Nabel et al. are equivalent to 293 cells taught in the specification (page 16, line 5) and can be used to make retroviral vectors as suggested by Nabel et al. In addition, the claims do not require release of the retroviral particle by budding. Furthermore, the cells of Miller et al. and Price et al. provide adequate guidance to obtain retroviral particles which bud from the packaging cells without lysing the cells. In fact, the PA317 packaging cells taught by Miller et al. are the packaging cells exemplified in the specification (page 28, line 9). Therefore, the combined teachings of Miller et al., Price et al. and Nabel et al. provide adequate guidance to obtain a packaging cell comprising a retroviral vector encoding SDI-1 as claimed.

Applicants argue one of skill would not have expected to get a stable retrovirus producing packaging cell by stable integration of a retroviral vector encoding SDI-1 because mitotic division of the packaging cell would be inhibited by SDI-1 protein. Applicants argument is not persuasive. Nabel et al. successfully demonstrates using 293 packaging cells to produce viral particles encoding SDI-1 (column 6, line 32). Nabel et al. does not teach SDI-1 expression prevents 293 packaging cell division or production of viral particles. Given the successful cell division of 293

packaging cells expressing SDI-1 and production of viral particles as taught by Nabel et al. taken with the suggestion of producing retroviral vectors provided by Nabel et al., one of ordinary skill would have had a reasonable expectation of obtaining packaging cells and retroviral particles comprising a retroviral vector encoding SDI-1. The packaging cell lines taught by Miller et al. and Price et al. would be expected to behave similarly to 293 packaging cells and would also provide a reasonable expectation to successfully divide when expressing SDI-1 and produce retroviral particles. Therefore, the art does not teach away from the claimed invention as asserted by applicants.

Claims 15, 16, 20-23 are free of the prior art because the art does not teach or suggest encapsulating packaging cells transfected with a retroviral vector encoding SDI-1 or treating a patient using such encapsulated packaging cells as claimed.

Conclusion

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson whose telephone number is (703) 305-0120. The examiner can normally be reached on Monday through Friday from 8:30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. The fax phone number for this Group is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

Michael C. Wilson

JOHN LEGUYADER
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GROUP 1800